REMARKS/ARGUMENTS

Claims 1-4 are pending. Favorable reconsideration is respectfully requested in view of the following remarks.

Rejection under 35 U.S.C. 102(e)

Claims 1 and 4 stand rejected under 35 U.S.C. 102(e) as being anticipated by Vidyadhar et al. US 6,649,765. This rejection is respectfully traversed.

The Examiner cites col. 4, example 2, of the '765 patent, and argues that the donepezil hydrochloride was dissolved in residue of free base concentrated from methylene dichloride solvent system adding a methanol and methanolic HCl mixture, then the solvents were removed to obtain a "solid", thus, anticipated the claims. The Examiner argues that a solid being silent about its crystallinity is noncrystalline or amorphous. (Office Action at page 2).

The Examiner also cites the CRC handbook, which defines amorphous as "having no definite order of crystalline structure". The Examiner concludes that therefore, if a solid was not defined to have "definitive crystalline order" is amorphous. The Examiner also cites Hackh's chemical dictionary is to show that the term "concentrate" chemically is the increase of solute content, thus, not removal of all solvent. The Examiner also cites Borchardt et al. which teaches that it is well recognized by chemists that the first isolated product before crystallization is ordinarily amorphous which is the Oswald's rule. (Office Action at page 2).

The Examiner further sets forth that a further continuation patent of US 6,649,765, the US 7,186,842, referred to the disclosure of the '765 material (see col. 2, lines 33-35) being made in Vidyadhar laboratory being *amorphous*. (Office Action at page 3).

However, in Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is

anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in US 6,649,765.

The Examiner's attention is directed to the fact that the claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of a process wherein donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent.

While the Examiner argues that a solid being silent about its crystallinity is noncrystalline or amorphous, the art cited by the Examiner does not stand for this proposition. The art cited by the Examiner simply defines the term "amorphous". It does not teach that a solid that was not defined to have "definitive crystalline order" is amorphous. In addition, the Borchardt reference cited by the Examiner only teaches that "When a newly synthesized compound is first isolated, it frequently may exist in amorphous form" (Borchardt at page 101; emphasis added). This teaches nothing regarding donepezil hydrochloride in particular, and does not teach that compounds are always isolated in amorphous form.

In addition, the disclosure of the '842 patent does not disclose that the product of the '765 patent is amorphous. The Specification of the '842 patent discloses ('842 at column 2, line 67 to

column 3, line 3):

> The present invention uses Donepezil oxalate (reported in our earlier U.S. application Ser. No. 10/879,816 and herein incorporated by reference) which is prepared by treating 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl] methyl piperidine compound (I) (Process for the Compound I is reported in our patent U.S. Pat. No. 6,649,765, herein incorporated as reference) with oxalic acid in suitable solvent.

The Specification of the '842 patent further discloses ('842 at column 2, line 67 to column 3, line 3):

> Donepezil base is prepared by a process as described in U.S. Pat. No. 6,649,765 B1 and is incorporated here as a reference.

In addition, the claims are directed to a process for the preparation of amorphous donepezil hydrochloride. The claimed process is not disclosed in the '765 patent. The claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent, which discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride, then dissolving the donepezil free base in methanol, followed by addition of hydrochloric acid. Therefore, the claimed process is not disclosed by the '765 patent.

Accordingly, reconsideration and withdrawal of the rejection of claims 1 and 4 under 35 USC 102(b) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijyadhar et al. US 6,649,765 in view of Imai et al. US 5,985,864. This rejection is respectfully traversed.

The Examiner sets forth that Vijyadhar et al.'765 disclosed an allegedly anticipatory process of the claims. The Examiner argues that the broader scope of claims 1 and 4 encompassing mixture of solvents beyond the residue amount or a different choice of combination; or the method of solvent removal being particularly vacuum drying or spray drying are prima facie obvious variation of the Vijyadhar et al. '765 process. The Examiner argues that it is conventionally known that donepezil hydrochloride are soluble in a variety of solvents (see Imai et al. '864 entire document), and vacuum or spray drying are conventional laboratory choices of solvent removing procedure. (Office Action at page 3).

The Examiner argues that one having ordinary skill in the art in possession of general laboratory skill and the Imai et al. '864 reference would be in possession of the instant claims because a proven process was disclosed by Vijyadhar '765, the optional choices of solvents wherein donepezil hydrochloride is soluble have been provided by Imai. The Examiner concludes that one having ordinary skill would pick and choose any of the solvent or mixture of solvents wherein donepezil hydrochloride is soluble for the process and employ anyone of the solvent removing technique for solvent reduction depending on resource availability. Picking and choosing an effect oriented condition in a chemical process is prima facie obvious in the chemical art, especially, such picking and choosing has been conventionally evidenced to be operable. In re Szumski 133 USPQ 551. (Office Action at page 3-4).

However, the claims are patentable over the combination of Vijyadhar et al. US 6,649,765 in view of Imai et al. US 5,985,864 reference for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of

law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Here, the claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. This deficiency is not addressed by the '864 Imai patent.

While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest a process for preparing amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent which is selected from the group

consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

The Examiner argues the motivation is provided in that one having ordinary skill in the art in possession of general laboratory skill and the Imai et at '864 reference would be in possession of the instant claims because a proven process was disclosed by Vidyadhar '765, the optional choices of solvents wherein donepezil hydrochloride is soluble have been provided by Imai, and that therefore, one having ordinary skill would pick and choose any of the solvent or mixture of solvents wherein donepezil hydrochloride is soluble for the process and employ anyone of the solvent removing technique for solvent reduction depending on resource availability. However, as set forth above, the '765 Vidyadhar patent does not teach or suggest donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent, and this is also not taught or suggested in the '864 Imai patent. Since the combination of the patents does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4 under 35 USC 103(a) is respectfully requested.

Rejection under 35 U.S.C. 103(a)

Claims 1-4 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al. US 4,895,841 or Vijyadhar et al. US 6,649,765, or Imai et al. US 5,985,864 in view of Lieberman et al. and Brittain. This rejection is respectfully traversed.

The Examiner argues that Sugimoto et al. (col. 34 example 4) or Vijyadhar et al.'765 (col. 4, example 2) disclose the process of making donepezil hydrochloride of the claims. Imai et al. '864 disclosed multiple variations of modifying the process of making donepezil hydrochloride

to obtain variations of crystalline and pure forms of the compound. (Office Action at page 4).

The Examiner admits that the difference between the prior art processes and the instant claimed process is that the products being made are crystalline or solids; using mixtures of more limited solvent combinations; and/or the method of solvent removal being particularly vacuum drying or spray drying. The Examiner argues that it is conventionally known that donepezil hydrochloride is soluble in a variety of solvents (see Imai et al. '864 entire document). The Examiner argues that it is a conventional teaching that amorphous is more desirable than crystalline form when formulation into pharmaceutical compositions (see Lieberman p.463 last paragraph) and the conventional process for obtaining amorphous material are spray drying or vacuum drying i.e. lyophilization. (Office Action at page 4).

The Examiner argues that one having ordinary skill in the art in possession of Sugimoto '841 or Vijyadhar '765 and the above references by Imai et al. '864, Lieberman and Brittain would be in possession of the instant claims because a proven process of making donepezil hydrochloride in a purified form was disclosed by Sugimoto '841, Vijyadhar '765 or Imai '864. The Examiner argues that one having ordinary skill in the art in possession of the purified crystalline or solid material of the compound donepezil hydrochloride would be motivated to prepare an amorphous form of the product because it is conventional state of the art that "*Theoretical considerations predict that amorphous solids* ***will*** *in general, be better absorbed than wil crystallne ones*" (citing Liberman p.463) and the procedure for obtaining amorphous forms have been conventionally well delineated using a spray drying or vacuum dryng process (Brittain). (Office Action at page 5).

The Examiner concludes that one having ordinary skill, being motivated by obtaining a

better absorbed amorphous form, would pick and choose any of the conventional combinations of solvents wherein donepezil hydrochloride is soluble, then, employ anyone of the solvent removing technique for solvent reduction depending on resource and availability, with the expectation of obtaining an "amorphous" form of the product; the claims would have been obvious because an ordinary skilled person "has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." KSR 82 USPQ2d 1385, 1390.

According to the Examiner the references provided:

--teaching from the art that donepezil hydrochloride is soluble in chlorinated solvent and alcohol specifically, methylene chloride and methanol;

--suggestion that spray dry a pharmaceutical product using a soluble solvent and spray drying procedure would produce an amorphous material;

--motivation that an amorphous material would give better dissolution. (Office Action at page 5).

However, not every element of the claims is taught or suggested in the combination of the references. As set forth above, the claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. Accordingly, there is not a teaching or suggestion in the '765 Vidyadhar

patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. In addition, there is not a teaching or suggestion in the '841 Sugimoto patent of a process in which donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent. Example 4 of the '841 Sugimoto patent as cited by the Examiner discloses donepezil base dissolved in methylene chloride, to which a 10% solution of hydrochloric acid in ethyl acetate is added, followed by concentration *in vacuo* to obtain a crystal, which was recrystallized from methanol/isopropyl ether. This deficiency is not addressed by the '864 Imai patent. While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride.

In addition, there is no motivation for one of skill in the art to alter the methods of the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the Lieberman and Brittain references to alter the methods as taught by the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the instantly claimed method.

Here, there is not a combination of prior art elements, since no reference, or combination of references, teaches or suggests a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. No reference or combination of references teaches or suggests such a method wherein the chlorinated solvent is chloroform, methylene

dichloride, carbontetrachloride or ethylene dichloride. In addition, Applicant has shown that there is not a reason why a person of ordinary skill in the art would be motivated to practice a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution.

Accordingly, reconsideration and withdrawal of the rejection of pending claims 1-4 is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.